BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Christina R. Bourne

eRA COMMONS USER NAME (credential, e.g., agency login): christinabourne

POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Oklahoma, Norman OK	BS	05/1997	Biochemistry
Oklahoma Medical Research Foundation and OU Health Sciences Center, Oklahoma City OK	PhD	10/2003	Biochemistry, Mol Biol and Structural Biology
OU Health Sciences Center, Oklahoma City OK	Postdoctoral Fellow	10/2007	Structural Virology

A. Personal Statement

I have more than 20 years of experience in biochemistry and structural biology, including 15 years working in microbiology and antibacterial development. My research interests focus on targeting drug-resistant and chronic bacterial infections, and I am pursue innovative new methods and novel targets to control bacterial growth. I have built my independent research program to study Toxin Antitoxin systems (publications a-c). There is a striking overlap between the bacterial "self" targets of these toxins, such as DNA gyrase, and potent anti-bacterial approaches, such as the highly valuable fluoroquinolone class of antibiotics. I am intrigued by the highly similar structures throughout the widespread RelE/ParE superfamily despite low sequence homology and divergent functions. Through studies to date, we have found different strengths of ParE toxin-induced phenotypes for homologous (30-80%) sequences, consistent with different levels DNA gyrase inhibition (publication a). We also identified different *in vitro* IC_{50} values for inhibition of the gyrase enzyme from *E. coli* versus that from *P. aeruginosa* by the same ParE toxin protein, suggesting a complex structure-function relationship (publication b). Recent work dissected a ParE toxin interface with its cognate ParD antitoxin and discovered how to weaken this interaction by manipulation of the disorder-to-order transition upon complexation (publication c, crystal structure 6xrw).

In conjunction with campus-wide efforts, I am committed to expanding my structural biology expertise to single particle reconstructions using cryo-electron microscopy, such as will be required to image ParE toxin proteins bound to DNA gyrase complexes. To facilitate this, participated in 6 weeks of embedded training through the NIH-funded Transformative High Resolution Cryo-Electron Microscopy Program. I have also established collaborations with three other independent principal investigators in Oklahoma to further local SPR studies. My team's current investigations build from our previously funded work in relating structure to function of ParE toxins, and has expanded through our current funding from the Department of Defense to formulate a central hypothesis of the structure-function relationship of how different sequence motifs found in ParE toxins differentially interact with and inhibit DNA gyrase.

a. Ames, J.R., Muthuramalingam M, Murphy, T., Najar F.Z., **Bourne C.R.** Expression of different ParE toxins results in conserved phenotypes with distinguishable classes of toxicity. Microbiol. Open. 2019 July; e902. PMID: 31309747; PMCID: PMC6813445.

b. Muthuramalingam M, White JC, Murphy, T., Ames, J.R., **Bourne C.R.** The toxin from a ParDE toxin-antitoxin system found in *Pseudomonas aeruginosa* offers protection to cells challenged with anti-gyrase antibiotics. Mol. Microbiol. 2019 Feb; 111(2):441. PMID: 30427086; PMCID: PMC6368863.

c. Snead, K.J., Moore, L.L., **Bourne, C.R.** ParD antitoxin hotspot alters a disorder-to-order transition upon binding to its cognate ParE toxin, lessening its interaction affinity and increasing its protease degradation kinetics. Biochemistry. 2022 Jan; 61(1):34. PMID: 34914387; PMCID: *in progress.*

Ongoing and completed projects that I would like to highlight:

U.S. Army, Department of Defense W81XWH2010121 (PI: C. Bourne) 02/20 – 05/23

"Unlocking the potential of bacterial ParE toxins: developing a blueprint for co-opting molecular time bombs that impact bacterial cell survival"
This project is examining the phenotypic outcomes for four human bacterial pathogens when their native chromosomal ParE toxins are over-expressed within the native host cells. A proof-of-concept study design will assess the efficiency of antitoxin removal from these ParE toxins in an *E. coli* host.
This award resulted directly from data collected during HR17-099, but the scope did not overlap with the previous OCAST award.

Oklahoma Center for the Advancement of Science HR17-099 (PI: C. Bourne) 07/17 – 3/21

"Targeting bacterial cell metabolism by manipulating toxin-antitoxin systems"
The goal of this project was to identify a strategy to interrupt the interactions of a chromosomally encoded ParE gyrase-inhibiting toxin with its cognate ParD antitoxin. Building from our crystal structure of the complex, this study demonstrated that point mutations could increase off-rates of antitoxin binding, thereby providing a novel therapeutic model for narrow-spectrum approaches.
Federal funding applications have been submitted using data from this completed OCAST HR award as preliminary data; while these were scored, resubmissions are pending.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022 - *current* Chair, Dept. of Chemistry and Biochemistry Graduate Committee
2022 – *(2023)* Elected member, Dodge Family CAS Graduate Academic Appeals committee
2022 - 2025 Secretary, Missouri Valley Branch, American Society of Microbiology
2021 - *current* Associate Professor, U. of Oklahoma, Dept. of Chemistry and Biochemistry, Norman, OK
2021 - (*2023)* U. of Oklahoma, Dept. of Chemistry and Biochemistry, Executive Comm. Member (elected)
2021 - *current* Member, User Review Committee, National Center for CryoEM Access and Training (NCCAT)
2017 - *current* Member (Chair, effective 2021), Advisory Committee, OU Biomolecular Structure Core Facility
2015 - *current* Member, OU Institutional Biosafety Committee
2014 - 2021 Assistant Professor, U. of Oklahoma, Dept. of Chemistry and Biochemistry
2011 - 2013 Member, BEI Resources Focus Group for Biodefense and High Containment Bacteria
2007 - 2013 Associate Research Scientist, Oklahoma State U., Center for Veterinary Health Sciences
2005 - 2007 American Cancer Society Postdoctoral Fellow, U. of Oklahoma Health Sciences Center

Other Experience and Professional Memberships

Ad Hoc manuscript reviewer (previous 4 years): *ACS Medicinal Chemistry, ACS Omega, Frontiers in Microbiology, Frontiers in Genetics, Genes, Journal of Biochemistry, mBio, Medicinal Research Reviews, Microorganisms, Molecular Microbiology, Nature Communications, Nature Reviews in Microbiology, Nucleic Acids Research, Protein Science, Structure, Toxins*

Proposal reviews (previous 4 years): French National Research Agency, BBSRC, US Army Research Office, NIH Special Emphasis Panel ZRG1 BST-M, U. of Missouri Research Board

Member, American Crystallographic Association (2001-present), American Society for Biochemistry and Molecular Biology (2003-present), American Society for Microbiology (2008-present), American Association for the Advancement of Science (2017-present)

2022 – *(2023)* Embedded training, National Center for CryoEM Access and Training (NCCAT), New York
2021 - *current* Member, Editorial Board, *Frontiers in Microbiology* section Microbial Physiology & Metabolism
2014 - 2017 Member, Editorial Board, *Scientific Reports*
2011 - 2017 Member, Editorial Advisory Board, *Journal of Molecular Recognition*
2015 Tech to Trek guest promoting science careers to young women, Southwestern Okla State Uni.
2015 Participant, BioCAT Advanced SAXS Training Course, Argonne National Laboratory

2000, 2014	Participant, RapiData X-ray Diffraction Data Collection and Structure Solving, Brookhaven National Laboratory
2012 - 2013	Mentor, Oklahoma State University Women's Mentorship Program
2010	Guest Scientist, Community outreach program "Born To Do Science"
2009	Participant, MolSoft2009 Workshop on Modern Drug Target Crystallography and Structure Based Drug Discovery, San Diego, CA

Honors

2022	OU Ed Cline Faculty Fellowship
2020	OU Nancy L. Mergler Faculty Mentor Award for Undergraduate Research
2020	Peggy Cotter Branch Travel Award, American Society of Microbiology
2018	OK - Louis Stokes Alliance for Minority Participation (LSAMP) Outstanding Faculty Mentor Award (Norman campus)
2014, 2015	VPR Summer Faculty Fellowship, University of Oklahoma
2005	Mary Horton Postdoctoral Fellowship, American Cancer Society
2005	Travel Grant, US National Committee for Crystallography
2003	Pauling Poster Prize, American Crystallographic Association
2001	Ludo Frevel Crystallography Scholarship, International Centre for Diffraction Data

C. Contributions to Science

1. **Toxin Antitoxin systems as targets to control bacterial growth:** Since joining the field of Toxin Antitoxin (TA) systems, my team has worked to characterize and compare the extensive interaction interfaces between the toxin and antitoxin proteins with an aim of manipulating them to alter bacterial growth. The shortened half-life of antitoxins also appears relevant to purified samples, and we have deduced an intrinsic degradation specifically at the toxin-binding region (e). Through our studies we also characterized RNase-type toxins and identified a promiscuous nuclease activity and species-specific toxicity for the YoeB type (crystal structure 6n90) (f,g).

   e. Snead, K.J., **Bourne C.R**. Intrinsic degradation of the Type-II antitoxin ParD from *Pseudomonas aeruginosa*. *bioRxiv* 2021 March; doi: 10.1101/2021.03.29.437564.

   f. Ames, J.R., McGillick, J., Murphy, T., Reddem, E., **Bourne, C.R.** Identifying a molecular mechanism that imparts species-specific toxicity to YoeB toxins. Front. Micro. 2020 May; 11:959. PMID: 32528435; PMCID: PMC7256200.

   g. McGillick, J., Ames, J.R., Murphy, T., **Bourne C.R.** A YoeB toxin cleaves both RNA and DNA. 2021 Sci. Reports *11:3592.* PMID: 33574407 PMCID: PMC7878887.

2. **New inhibitors of bacterial biosynthetic folate pathway:** I have published extensive SAR studies to characterize inhibitors derived from the structure of the antibiotic trimethoprim, including whole cell MIC measurements, *in vitro* enzyme activity inhibition, and three-dimensional structure determinations. This work produced structures of the dihydrofolate (DHFR) from three different bacteria, resulting in 13 deposited crystal structures (publications h, i). These studies have expanded in my independent lab at OU (publication k, 7 deposited crystal structures).

   h. **Bourne CR**, Wakeham N, Nammalwar B, Tseitin V, Bourne PC, Barrow EW, Mylvaganam S, Ramnarayan K, Bunce RA, Berlin KD, Barrow WW. Structure-activity relationship for enantiomers of potent inhibitors of *B. anthracis* dihydrofolate reductase. Biochim Biophys Acta. 2013 Jan;1834(1):46. PMID: 22999981; PMCID: PMC3530638.

   I. **Bourne CR**, Wakeham N, Webb N, Nammalwar B, Bunce RA, Berlin KD, Barrow WW. The structure and competitive substrate inhibition of dihydrofolate reductase from *Enterococcus faecalis* reveal restrictions to cofactor docking. Biochemistry. 2014 Feb 25;53(7):1228. PMID: 24495113; PMCID: PMC3985486.

   j. Muddala, P.N., White, J.C., Nammalwar, B., Pratt, I., Thomas, L.M., Bunce, R.A., Berlin, K.D., **Bourne, C.R.** Inhibitor design to target a unique feature in the folate pocket of *Staphylococcus aureus* dihydrofolate reductase. 2020 Eur. J. Med. Chem. 200:112412. PMID: 32502861; PMCID: PMC7932028.

3. **A new strategy for antiviral therapy using misdirection of capsid assembly:** As a post-doc I contributed to a novel approach to anti-viral therapies by altering the assembly pathway of the Hepatitis B virus capsid assembly. Using biophysical measurements and biochemical assays, we determined this compound mis-directed HBV assembly (publication k) and I identified a lab-derived genotype that could mimic these effects (publication l). I was awarded a fellowship from the American Cancer Society to pursue structural studies, and these resulted in two crystal structures (2g33, 2g34) identifying the binding pocket for these compounds, contributed to structure-guided compound modifications, and subsequently tested derivatized compounds to validate the compound orientation (publications m, n).

   k. Stray SJ, **Bourne CR**, Punna S, Lewis WG, Finn MG, Zlotnick A. A heteroaryldihydropyrimidine activates and can misdirect hepatitis B virus capsid assembly. Proc Natl Acad Sci U S A. 2005 Jun 7;102(23):8138. PMID: 15928089; PMCID: PMC1149411.

   l. **Bourne CR**, Katen SP, Fulz MR, Packianathan C, Zlotnick A. A mutant hepatitis B virus core protein mimics inhibitors of icosahedral capsid self-assembly. Biochemistry. 2009 Mar 3;48(8):1736. PMID: 19196007; PMCID: PMC2880625.

   m. **Bourne CR**, Finn MG, Zlotnick A. Global structural changes in hepatitis B virus capsids induced by the assembly effector HAP1. J Virol. 2006 Nov;80(22):11055. PMID: 16943288; PMCID: PMC1642186.

   n. **Bourne C**, Lee S, Venkataiah B, Lee A, Korba B, Finn MG, Zlotnick A. Small-molecule effectors of hepatitis B virus capsid assembly give insight into virus life cycle. J Virol. 2008 Oct;82(20):10262. PMID: 18684823; PMCID: PMC2566253.

4. **Structure and function of human antibodies:** My graduate work focused on mechanisms of protein crystal growth and their application to the structural properties of human antibodies. I participated in studies conducted on flight missions STS-95 and STS-107 to evaluate the effect of microgravity on protein crystal quality (publication o, p). Other work identified an inherent proteolytic capacity of a subset of neoplastic-derived human IgM antibodies (publications q, r, crystal structure 2agj), a revolutionary finding that is still an active area of research, for example in the Ramsland lab at RMIT, Melbourne, AU.

   g. Alverado UR, **DeWitt CR**, Shultz BB, Ramsland PA, Edmundson AB. A method for growing protein crystals in capillary tubes. J Cryst Growth 2001; 233:407-414.

   h. Terzyan SS, **Bourne CR**, Ramsland PA, Bourne PC, Edmundson AB. Comparison of the three-dimensional structures of a human Bence-Jones dimer crystallized on Earth and aboard US Space Shuttle Mission STS-95. J Mol Recognit. 2003 Mar-Apr;16(2):83. PMID: 12720277.

   i. Ramsland PA, Upshaw JL, Shultz BB, **DeWitt CR**, Chissoe WF, Raison RL, Edmundson AB. Interconversion of different crystal forms of Fabs from human IgM cryoglobulins. J Cryst Growth 2001; 232:204-214.

   j. Ramsland PA, Terzyan SS, Cloud G, **Bourne CR**, Farrugia W, Tribbick G, Geysen HM, Moomaw CR, Slaughter CA, Edmundson AB. Crystal structure of a glycosylated Fab from an IgM cryoglobulin with properties of a natural proteolytic antibody. Biochem J. 2006 May 1;395(3):473. PMID: 16422668; PMCID: PMC1462693.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/10usXwuC15FAk/bibliography/47974641/public/?sort=date&direction=descending